(12) UK Patent Application (19) GB (11) 2 078 696 A

(21) Application No 8115770
(22) Date of filing 22 May 1981
(30) Priority data
(31) 55/070060
(32) 28 May 1980
(33) Japan (JP)
(43) Application published
13 Jan 1982
(51) INT CL³
C01F 11/00
(52) Domestic classification
C1A 424 510 530 D37
D80 G47 G47D37 G47D80
PG2
(56) Documents cited
GB 1554943
GB 1484781
GB 1421531
GB 1004352
(58) Field of search
C1A
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(54) **Porous Calcium Phosphate Body**

(57) A filler for defects or hollow portions of bones comprises a porous body of a calcium phosphate compound, such as hydroxyapatite. The pores in the body are formed by a three-dimensional network of void channels, each channel being of varying width along its length. The maximum width of any channel is 3.00 mm and the minimum width is 0.05 mm. The porosity of the porous body is from 40% to 97%, providing a filler into the void channels of which bone forming constituents of living bodies can easily penetrate and create new bone growth.

SPECIFICATION

Filler for Implanting in Defects or Hollow Portions of Bones

The present invention relates to an inorganic filler to be used to fill in defects or hollow portions of bones formed by operations to remove bone tumor or other causes in the bones of living bodies, to promote the formation of new bone tissue at the filled portion and to coalesce with the bone tissue after the injured portion is completely cured.

In the surgical or orthopedic field, defects or hollow portions of bones are frequently formed by highly complicated fractures or operations to remove bone tumor, and such defects or hollow portions should be cured by symphysis. In a prior art method, a cancellous bone is taken up from flank bones or other bones of the patient to be filled in the injured portion of bone so as to promote the cure of bone tissue. However, this prior art method is disadvantageous in that the patient suffers a greater pain and cumbersome labours are necessitated in the operation, since a bone tissue other than the injured portion is taken out for use. Moreover, a sufficient amount of autoplastic bone cannot be always taken up from the patient's body for filling in a large defect or hollow portion of bone, and a certain substitute material is required to supplement the shortage of the required bone tissue in such a case.

Other than the method of autoplastic filling, there are methods of homogeneous bone implantation and heterogeneous bone implantation. As to the homogeneous bone implantation method, the use of frozen bones and decalcified bones have been investigated but have not yet reached the stage of clinical practice. In the heterogeneous bone implantation method, a so-called keel bone, which is prepared by removing proteins from bones of cattle, is used in some cases. However, both of these known methods are not only accompanied with foreign body reactions but also lack osteogenic capacity, so that the post-operational course is not always good.

Accordingly, there is an increasing demand for an artificial filler material for filling or implanting in defects or hollow portions of bones. This must have a good compatibility with the living body and a high osteogenic capacity to promote the bone-forming reaction at and around the filled portion so as to accelerate curing of the structure and functioning of the injured bone tissue.

Various metals and plastics materials have hitherto been used as the substitute materials for hard tissues of the living body. However, these conventional materials are apt to dissolve or otherwise deteriorate under the severe environment of the living body and are often accompanied by poisonous actions or foreign body reactions. For these reasons, ceramics, which have improved compatibilities with living body, have been increasingly used in recent years. Inter alia at the latest time, an artificial bone and an artificial radix dentis comprising a sintered body or a single crystalline structure of alumina, carbon, calcium tertiary phosphate ($Ca(PO_4)_2$) or hydroxyapatite ($Ca_5(PO_4)_3OH$) have been proposed. It has been reported that these are excellent in their compatibility with the living body.

Although it has been tried to implant the above mentioned sintered body or single crystalline structure in a defect or hollow portion of bone to be remedied, difficulties are encountered when the sintered body or single crystalline structure has to be machined to create a snug fit into the bone defect which may have a complicated shape rather than a simple and constant shape. Moreover, even if such a sintered body or single crystallite structure could be implanted in a defect, absorption of bone tissue would occur at the vicinity of the implanted portion since the sintered body or single crystalline structure is generally substantially harder than the surrounding bone tissue to give a stimulus to the surrounding living tissue. As a result, loosening or other problems occur, so that a sintered body or single crystalline structure of the aforementioned kind has not yet reached the stage of practical use.

It has been proposed to make a porous body of a sintered material by the mechanical method of first moulding a mixture of the powder to be sintered and a portion of combustible fibres, followed by sintering so as to obtain a porous body having a shape which can be snugly fitted in a defect or hollow portion of bone. However there are two serious practical problems. The first is the difficulty of moulding mixtures with a combustible fibre content high enough to produce a sufficiently porous sintered body. The second is that the fragility of a porous sintered ceramic body increases and its machinability decreases, as the total pore volume of the sintered body increases. Thus sintered bodies of ceramics having sufficiently high porosities have not yet been manufactured commercially. Because of the lack in porosity due to the difficulties as aforementioned bone forming constituents can scarcely penetrate the rather solid filler, so that coalescence of the filler with the living tissues to form new bone is very slow.

According to the present invention, there is provided a filler for filling in defects or hollow portions of bones, comprising a porous body of a calcium phosphate compound in which a plurality of channels communicate with each other to form a three-dimensional network of voids, wherein each channel has along its length a non-constant width of between 3.00 mm and 0.05 mm, and the porosity of the body is from 40% to 97%.

It has been found that the growth of new bone is promoted by a filler according to the invention, with the new bone being grown in a defect or hollow portion of bone from the portion at which the filler is in contact with the old bone.

The calcium phosphate compounds which may be used in the present invention include calcium

secondary phosphate ($CaHPO_4$) and its dihydrate ($CaHPO_4 . 2H_2O$), calcium tertiary phosphate ($Ca_3(PO_4)_2$), hydroxyapatite ($Ca_5(PO_4)_3OH$), calcium tetraphosphate ($Ca_4O(PO_4)_2$), calcium undecaoxo-tetraphosphate ($Ca_3P_4O_{11}$), calcium metaphosphate ($Ca(PO_3)_2$), calcium pyrophosphate ($Ca_2P_2O_7$) and calcium dihydrogenphosphate monohydrate ($Ca(H_2PO_4)_2 . H_2O$). These compounds may be used individually or in a form of mixture containing two or more of them. Amongst the compounds set forth above, calcium tertiary phosphate ($Ca_3(PO_4)_2$), hydroxyapatite ($Ca_5(PO_4)_3OH$) and calcium tetraphosphate ($Ca_4O(PO_4)_2$) are preferable compounds, since growth of new bone is particularly accelerated when any one or more of these three compounds is used. The most preferable compound to promote growth of new bone is hydroxyapatite, particularly hydroxyapatite which is baked at a temperature of higher than 500°C, preferably 700 to 1250°C. The upper limit temperature of baking operation is not critical but should be controlled not to exceed the decomposition temperature of hydroxyapatite. The calcium phosphate compounds used in the present invention may be either artificially synthesized compounds produced by any known process or compounds of natural original obtained from human or animal bones.

In the filler of the invention, the internal areas of the channels or void cavities is increased so that increased quantities of calcium and phosphoric ions are dissolved internally of the porous body. An increase in the dissolved quantities of calcium and phosphoric ions is one of the principal advantages of the present invention. As a result of this increase, the formation of new bones is commenced rapidly with new bones growing on the surfaces of bone forming tissues, including collagen, which have penetrated into the channels or cavities. Since the width of each channel varies randomly along its length, numerous concave and convex portions, providing recesses and projections, are formed along the internal surface of each channel. The present invention is based on the observation that there is a tendency for the bone forming substances to adhere initially to or at the vicininities or projections in the channels while being accompanied with osteoblasts, and that new bones begin to grow from the projections at which the bone forming substances and osteoblasts adhere. In addition, in a filler according to the present invention the void cavities or channels in the porous body communicate with each other to form a three-dimensional network. Accordingly, the bone forming constituents entering the void cavities can penetrate deeper into and finally throughout all regions of the three-dimensional network. Naturally it will be understood that although the void cavities or channels communicate with each other to an extent that a generally cross-linked and three-dimensional structure of void channels is formed through the porous body, some of the channels or cavitities may be closed, resulting in a few closed cells.

The maximum dimension width of each channel in any direction is less than 3.00 mm, and the minimum dimension thereof is more than 0.05 mm. It has been found that if the maximum width were to exceed 3.00 mm, a prolonged period of time would be required for the bone tissue of autoplasty or self-origin to grow and fill in the cavities. On the other hand, if the minimum width were to be less than 0.05 mm, penetration of bone forming constituents, such as collagen, into the cavities of the porous body would be prevented or blocked at the too narrow portions. As a result, the bone forming constituents would not proceed or grow through the blocked or clogged portions, leading to formation of hollow portions in which new bone growth does not occur.

The porosity of the filler according to this invention is from 40% to 97% pore volume. If the porosity were less than 40%, an excessively long time would be required for the bone tissue and the filler to coalesce with each other to form a unified body. Moreover, the machinability of such a dense filler would be reduced to an extent to make it impossible to shape the filler to be snugly fitted in a defect or hollow portion of bone by machining. On the other hand, if the porosity were to exceed 97%, the bulk or volume of newly formed bone would be deficient due to lack of filler material, resulting in an unsatisfactory curing effect. Namely, a longer time would be required for the remedy of the impaired bone portion because the quantity of calcium phosphate implanted would be too small.

The filler according to the present invention may be prepared by a process comprising first impregnating a slurry of a calcium phosphate compound into an organic porous body having a substantially continuous cavity or cavities and having a three-dimensional network structure, with the width distribution required in the final filler. The slurry of calcium phosphate compound is then dried, and the material of the organic porous body removed by heating or other means.

When the filler according to the present invention is filled or implanted in a defect or hollow portion of bone, living bone forming constituents such as collagen and body liquids will penetrate into the pores of network structure of the porous body until they are diffused uniformly throughout the network structure. The filler of the invention does not cause any foreign matter reaction and facilitates rapid formation of new bone. Furthermore, the filler *per se* is absorbed in the living body and gradually by the autoplastic bone.

The filler of the invention can be used not only for filling in defects or hollow portions of bones formed by surgical or arthroplastry operation, but also for filling cavities formed by dental caries or by a tooth extraction operation or in a defect caused by alveolar pyorrhea.

Examples

The following Examples illustrate the invention.

Example 1

Slurries of calcium tertiary phosphate, calcium tetraphosphate and hydroxyapatite were prepared. Each of the slurries of calcium tertiary phosphate and calcium tetraphosphate was synthetically prepared by the wet process followed by pulverization in a pot mill for over 40 hours in the wet state. The slurry of hydroxyapatite was prepared by the wet process. A porous substrate body made of an organic material and having continuous pores was impregnated with each of said three slurries. The slurry impregnated in the porous body was dried and then baked at 1000°C for three hours to burn away the organic material. As a result, a porous body made of each calcium phosphate compound was formed.

From each calcium phosphate compound, five kinds of porous bodies were prepared by controlling the dimensions of channels of non-constant width which form the pores within the body. The porous body included pores having a maximum width of 5 mm and a minimum width of 3 mm. The second to fourth porous bodies included pores having, respectively, a maximum width of 3.0, 0.5 and 0.07 mm and a minimum width of 1.5, 0.2 and 0.05 mm. The fifth porous body included pores having a maximum width of 0.1 mm and a minimum width of 0.007 mm. The porosities of all of these porous bodies ranged within 68 to 73%.

Each porous body was filled or implanted in a defect of bone (about 6mmϕ×5 mmL) artificially scooped out of a femure of a living dog which was bred after then, and the course of healing and new bone growth was observed. As of three weeks after the implantation operation, new bones were formed in each of the porous bodies except the fifth (which was the body including pores having a maximum width of 0.01 mm and a minimum width of 0.007 mm. However, in the fifth porous body no appreciable formation of new bones was observed in the void cavities internally of the pores.

Observation after three months from the implantation operation revealed that large quantities of new bones had been formed in the void channels of the second to fourth porous bodies. In these three porous bodies, almost all of the filler materials were substituted by the living bone tissues and the defects were coalesced practically to form a unified continuation of the neighbouring unimpaired bone tissue. Scattering void spaces were observed here and there in the pores of the first and fifth porous bodies.

Example 2

Similarly to Example 1, using hydroxyapatite synthesized through the wet process, four different porous bodies were prepared having respective porosities of 20%, 40%, 70% and 97%. The maximum width of the channels providing the pores of the respective porous bodies was controlled to be within the range of 2 to 1 mm, and the minimum width thereof was controlled to be within the range of 0.8 to 0.1 mm. Each of the resulting porous bodies was implanted in an artificially scooped defect (4 mmϕ×5 mmL) of a femur of a living dog, and the courseof healing and new bone growth was observed.

An attempt was made to prepare a porous body having a porosity of 99% according to a similar process, but this body collapsed due to its lack of inherent rigidity during the step of machining it to be snugly received by the cavity of the defect.

The porous body having a porosity of 20% was also difficult to shape at this step of machining. On examination three months after the implantation, it was found that the bodies had coalesced with the living bone tissues except in the case where a porous body having a porosity of 20% was used. In this latter case the filler has been adhered to the bone tissue at the zones contacting with the surrounding original living bone tissues, but no appreciable coalescence was observed internally of the channels of the porous body.

Example 3

Similarly to Example 1, using hydroxyapatite synthesized by the wet process, six porous bodies were prepared by impregnating a hydroxyapatite slurry into pores of substrate bodies of an organic material followed by baking to burn away the organic material. Baking was effected for an hour at a temperature of 300°C, 500°C, 700°C, 1000°C, 1250°C and 1350°C, respectively. The maximum width of the void channels of the resulting porous bodies was within the range of 0.5 to 0.4 mm, and the minimum width thereof was within the range of 0.3 to 0.2 mm. Each porous body was implanted in an artificially scooped defect (4 mmϕ×5 mmL) of a femur of a living dog, and the course of healing and new bone growth was observed.

It was observed that new bones had been formed in the void channels of all of the respective porous bodies after a lapse of three weeks after implantation. However, there was substantial new bone growth in the porous bodies which had been baked at temperatures higher than 500°C, and particularly remarkable formation or growth of new bones was observed in the channels of porous bodies which had been baked at a temperature of from 700°C to 1250°C.

Claims

1. A filler for filling in defects or hollow portions of bones, comprising a porous body of a calcium phosphate compound in which a plurality of channels communicate with each other to form a three-dimensional network of voids, wherein each channel has along its length a non-constant width of between 3.00 mm and 0.05 mm, and the porosity of the body is from 40% to 97%.

2. A filler according to claim 1, wherein the calcium phosphate compound is calcium secondary phosphate ($CaHPO_4$), calcium secondary phosphate dihydrate ($CaHPO_4 . 2H_2O$), calcium tertiary phosphate ($Ca_3(PO_4)_2$), hydroxyapatite ($Ca_5(PO_4)_3OH$), calcium tetraphosphate ($Ca_4O(PO_4)_2$), calcium hendecaoxo-tetraphosphate ($Ca_3P_4O_{11}$), calcium methaphosphate ($Ca(PO_3)_2$) calcium pyrophosphate ($Ca_2P_2O_7$), calcium dihydrogenphosphate monohydrate ($Ca(H_2PO_4)_2 . H_2O$) or a mixture of two or more of the above compounds.

3. A filler according to claim 2, wherein the calcium compound is calcium tertiary phosphate, hydroxyapatite, calcium tetraphosphate or a mixture therof.

4. A filler according to claim 3, wherein the calcium compound is hydroxyapatite that has been baked at a temperature of higher than 500°C.

5. A filler according to claim 4, wherein the hydroxyapatite has been baked at a temperature of from 700°C to 1250°C.

6. A filler according to any of the preceding claims, wherein the calcium phosphate compound has been synthesized by the dry process.

7. A filler according to any of claims 1 to 5, wherein the calcium phosphate compound has been synthesized by the wet process.

8. A filler according to any preceding claim wherein the calcium phosphate compound has been prepared from bone tissue.

9. A filler according to claim 1, substantially as disclosed in any of the Examples herein.

Printed for Her Majesty's Stationery Office by the Courier Press, Leamington Spa, 1982. Published by the Patent Office, 25 Southampton Buildings, London, WC2A 1AY, from which copies may be obtained.